

Predictive Role Of Body Composition Parameters In Operable Breast Cancer Patients Treated With Neoadjuvant Chemotherapy

This article was published in the following Dove Press journal:
Cancer Management and Research

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Background: Fat tissue is strongly involved in BC tumorigenesis inducing insulin resistance, chronic inflammation and hormonal changes. Computed tomography (CT) imaging instead of body mass index (BMI) gives a reliable measure of skeletal muscle mass and body fat distribution. The impact of body composition parameters (BCPs) on chemosensitivity is still debated. We examined the associations between BCPs and tumor response to neoadjuvant chemotherapy (NC) in patients treated for operable breast cancer (BC).

Methods: A retrospective review of BC patients treated with NC in Modena Cancer Center between 2005 and 2017 was performed. BCPs, such as subcutaneous fat area (SFA), visceral fat area (VFA), lumbar skeletal muscle index (LSMI) and liver-to-spleen (L/S) ratio were calculated by Advance workstation (General Electric), software ADW server 3.2 or 4.7. BMI and BCPs were correlated with pathological complete response (pCR) and survival outcomes.

Results: 407 patients were included in the study: 55% with BMI < 25 and 45% with BMI ≥ 25. 137 of them had pre-treatment CT scan images. Overweight was significantly associated with postmenopausal status and older age. Hormonal receptor positive BC was more frequent in overweight patients ($p < 0.05$). Postmenopausal women had higher VFA, fatty liver disease and obesity compared to premenopausal patients. No association between BMI classes and tumor response was detected. High VFA and liver steatosis were negative predictive factors for pCR (pCR rate: 36% normal VFA vs 20% high VFA, $p = 0.048$; no steatosis 32% vs steatosis 13%, $p = 0.056$). Neither BMI classes nor BCPs significantly influenced overall survival and relapse-free survival.

Conclusion: Visceral adiposity as well as steatosis were closely involved in chemosensitivity in BC patients treated with NC. Their measures from clinically acquired CT scans provide significant predictive information that outperform BMI value. More research is required to evaluate the relationship among adiposity site and survival outcomes.

Keywords: BMI, fat tissue, sarcopenia, pathological complete response, breast cancer

Introduction

Obesity is a known risk factor for various health disorders, including breast cancer (BC).¹ Obesity is generally evaluated using body mass index (BMI), that is an indirect measurement of adipose tissue, calculated as weight in kilograms divided height in meters squared. BMI cannot account for differences in fat distribution and cannot distinguish between adipose tissue and muscles. In fact, low BMI can mask excess of adiposity such as high BMI can mask low muscularity. Computed tomography (CT) imaging can be a useful tool for a direct measure of body fat

distribution distinguishing among visceral, subcutaneous, internal fat tissue (mostly in the liver) and skeletal muscle mass.²

Several studies highlighted the association between obesity and poor prognosis in BC patients.³ It is well known that women with BC, who are overweight or gain weight after diagnosis, have a greater risk for recurrence and death.³ Moreover, not only the excess of adiposity, but also sarcopenia (low skeletal muscle mass) seems to be a negative prognostic factor for death and recurrence in patients with non-metastatic BC.⁴ Biologically, fat cells can produce inflammatory cytokines (IL-6 and TNF- α), growth factors (insulin growth factor receptor), aromatase and adiponectin.⁵ These molecules increase the level of leptin and endogenous sex steroids determining chronic inflammation and insulin resistance.⁵ Given these facts, adipose tissue may influence treatment sensitivity. Only two studies, with a small sample size, have examined the relationship between body composition and neoadjuvant treatment sensitivity in BC women, providing controversial results.^{6,7} Our goal was to examine associations between measure of body composition parameters (BCPs), considering adiposity and sarcopenia, and response to neoadjuvant chemotherapy (NC) in patients treated for operable BC.

Patients And Methods

Patient Population

We performed a retrospective review of the electronic medical records of all patients treated with NC for early BC in Modena Cancer Center between 2005 and 2017. All the patients with a histologically proven diagnosis of BC (stage I–III) treated with primary chemotherapy either within clinical trials or on the basis of standard guidelines were included. Patients needed weight and height available and/or pre-treatment CT scan images. No other eligibility/exclusion criteria were applied. Tumor-specific characteristics, including cancer stage, grade and tumor subtypes, were collected. Tumor subtypes were defined as follows: human epidermal growth factor receptor 2 (HER2) positive BC (HER2 status was reported as positive or negative according to IHC 3+ or HIS amplification), hormone receptor positive BC (estrogen and/or progesterone receptors expression >1% and HER2 negative) and triple negative (TN) BC (hormone receptor and HER2 negative). NC was given according to the standard recommendation, dose reduction or drug discontinuation were applied in case of

toxicity according to clinician's choice. Data about patient characteristics' such as age, menopausal status, weight and height at the beginning of NC were collected. Responses to NC were collected too. Pathological complete response (pCR) was defined as complete disappearance of invasive tumor in the breast and axillary lymph nodes.

Body Mass Index (BMI)

According to the international classification of body mass index (BMI), patients were categorized into two main classes: normal weight (BMI < 25) and overweight (BMI \geq 25). Moreover, in the subgroup of normal weight patients, women with BMI <18.5 were classified as underweight (BMI < 25) while overweight patients with BMI \geq 30 were considered obese.

Body Composition Parameters (BCPs)

For patients with available CT scan images taken at the time of the initial treatment, BCPs were calculated by Advance workstation (General Electric), software ADW server 3.2 or 4.7. The cutoff points used for classifying BCPs were based on data in the literature.^{6,8} Radiologists, who performed the BCPs measures, were blinded for clinical data. We evaluated subcutaneous fat area (SFA, cm²), visceral fat area (VFA, cm²), lumbar muscle cross-sectional area (LMCA, m²) and liver steatosis (L/S ratio). In particular, the cut-off for high SFA and VFA was 100: VFA and SFA < 100 meaning normal visceral or subcutaneous adiposity while VFA or SFA \geq 100 meaning high visceral or subcutaneous adiposity, respectively. Using BMI and VFA value, the presence of Obesity Disease, defined as BMI \geq 25 and VFA \geq 100 was evaluated too. The lumbar muscle cross-sectional area (LMCA, m²) was used as a measure of total body skeletal muscle mass including psoas, paraspinal and abdominal wall muscles. In order to adjust the LMCA according to patient stature, we calculated the lumbar skeletal muscle index (LSMI, cm²/m²): total L3 skeletal muscle mass/body surface area. The cut-off value for LSMI was 38.5: patients with LSMI < 38.5 were sarcopenic while those with LSMI \geq 38.5 were normal. Finally, the presence of liver steatosis was considered as a measure of internal fat distribution. The CT liver-to-spleen ratio (L/S ratio) was used for fatty liver analysis. Fatty liver was defined as L/S ratio <1.

Statistical Analysis

Baseline clinical characteristics were compared between BMI subgroups (<25 vs \geq 25) by chi-square test for

categorical variables (i.e. menopausal status, BC subtypes, grade, neoadjuvant chemotherapy, type of surgery, stage) and by Wilcoxon Mann–Whitney test for continuous variables (i.e. age at diagnosis). The association between BCPs and menopausal status and the association between BCPs and pathological complete response were evaluated through the chi-square test. The association between BCPs and pCR was assessed by calculating odds ratio and their 95% confidence intervals through univariate logistic regression.

Overall survival (OS: defined as the time from diagnosis of BC to death/last follow-up), and relapse-free survival (RFS: defined as the time from the date of the diagnosis to the date of the first documented relapse or death) were assessed. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were obtained through univariate and multivariate Cox models considering BMI subgroups, BCPs and pathological complete response.

All analyses were performed using STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

A total of 407 patients were included in the study, 137 of them had pre-treatment CT scan image available for BCPs analysis (Figure 1). Overall, 225 were normal weight with a BMI score under 25 compared to 182 (45%) overweight. Specifically, in the subgroup of overweight women 37% (68) were obese. Only 8 patients were underweight. Patient, tumor and treatment characteristics stratified by BMI subgroups are listed in Table 1. The two cohorts of patients were well balanced according to treatment administered, type of surgery,

grade and stage of disease. There was no association between clinical stage, nuclear grade, neoadjuvant chemotherapy regimen, type of surgery and BMI subgroups (p =not significant). Overall, 75% of patients received anthracycline-taxane-based regimen, 5% taxane-based chemotherapy, 9% anthracycline-based regimen and 8% platinum-based regimen. Of note, 7% of overweight patients received a chemotherapy dose reduction due to their high body surface area. Considering patients' characteristics, overweight was significantly associated with postmenopausal status and older (≥ 65 years) age. Particularly, 37% of premenopausal women were overweight vs 53% of postmenopausal women (Table 1). Considering tumour subtypes and BMI, hormonal receptor positive (HR+) tumors were more frequent in overweight women ($p < 0.05$). Regarding BCPs, most of the patients (94%) had high SFA while VFA was normal in most than half of them. Overall, 34% of women had criteria for Obesity Disease. Moreover, liver steatosis was detected in 18% of women. Finally, 48 patients were sarcopenic, 8 of them with sarcopenic overweight. We found no detectable difference between body fat distribution parameters and tumor subtype. On the contrary, postmenopausal status was significantly associated with high VFA, fatty liver disease and obesity (Table 2).

Overall, 25% of patients achieved pCR. In particular, 57% of them (59 patients) were normal/underweight vs 43% (44) overweight according to BMI classification (p =not significant) (Table 1). On the contrary, high visceral fat and liver steatosis were negative predictive factors for tumor response to neoadjuvant chemotherapy ($p \leq 0.05$) (Table 3 – Figure 2). In particular, in the subgroup of patients with pCR, 67% had normal visceral fat and 92% absence of fatty liver disease, respectively. No statistical significant correlation between BCPs and pCR according to BC phenotype was detected.

At the time of the analysis, 25 patients (6%) had died and 33 (8%) had experienced a recurrence: 7 (3.8%) and 12 (6.5%) in overweight subgroup vs 18 (8%) and 21 (9%) in normal weight cohort, respectively. Neither BMI classes nor BCPs distribution significantly influenced overall survival and relapse-free survival. Only pCR was significantly associated with better survival outcomes in univariate analysis. As expected, patients with pCR have better OS (HR 0.37; 95% CI, 0.18 to 0.77, $p = 0.008$) and RFS (HR, 0.34; 95% CI, 0.16 to 0.74, $p = 0.007$) compared to patients with residual cancer disease after systemic therapy.

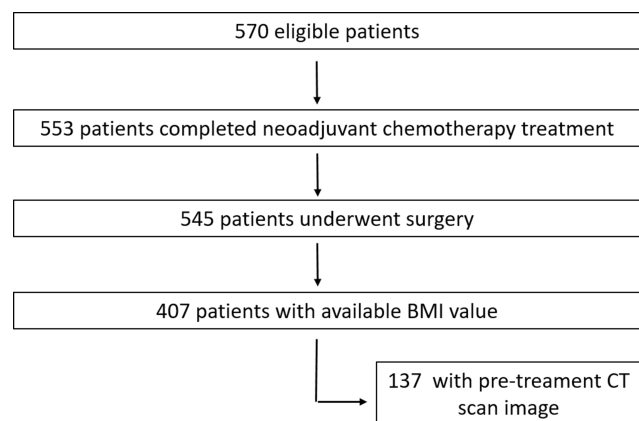


Figure 1 Flowchart of the study population.

Table 1 Patient And Clinical Characteristics By BMI Value Among Women Treated With Neoadjuvant Chemotherapy

Clinical Characteristics	All Patients		BMI < 25 kg/m ²		BMI ≥ 25 kg/m ²		p Value
Patients	407		225 (55%)		182 (45%)		
	n	%	n	%	n	%	
Age, median (range)	50 (25–80)		47 (25–80)		54 (29–80)		<0.0001
Menopausal status							0.001
Premenopause	209	52	133	59	77	42	
Postmenopause	198	48	92	41	105	58	
BC subtypes							0.052
HR+	155	38	75	33	80	44	
HER2+	148	36	84	37	64	35	
TN	104	26	66	30	38	21	
Grading							0.941
I–2	43	11	24	11	19	10	
3	364	89	201	89	163	90	
Neoadjuvant chemotherapy							0.088
Anthracycline	34	9	17	7	17	9	
Anthracycline + taxane	307	76	171	76	136	75	
Taxane	19	5	6	3	13	7	
Platinum-based regimen	26	8	18	8	8	5	
Other	19	5	13	6	6	3	
Unknown	2	1	0	0	2	1	
Type of surgery							0.688
Mastectomy	208	51	117	52	91	50	
Lumpectomy	199	49	108	48	91	50	
Stage							0.333
I	4	1	3	2	1	<1	
II	295	73	168	74	127	70	
III	108	26	54	24	54	30	
pCR							0.637
Yes	103	25	59	26	44	24	
No	304	75	166	74	138	76	

Note: Significant P-value is shown in bold.

Discussion

The achievement of pCR is a known prognostic factor in BC patients treated with NC. Several biological and clinical parameters influence tumor response to chemotherapy.^{9–11} Body fat tissue seems to be one of these factors. Fat tissue promotes cancer progression by increasing cell proliferation, cell survival and metastatic processes.⁵ Adipose tissue determines a dysregulation of several metabolic pathways by a continuous crosstalk between fat tissue and cancer cells.¹² Adipocytes modify tumor microenvironment inducing insulin resistance and inflammation by the production of leptin, adiponectin, plasminogen activator inhibitor-1 and vascular endothelial growth factor.¹³ In particular, finding from a recent clinical

studies review, suggested how the influence of adipose tissue on cancer development depends on the type of fat too. Visceral adipose tissue seems to be more bio-energetically active and with more pro-cancer activity than subcutaneous adipose tissue.¹⁴ CT scan images are a useful tool to assess information on body fat distribution and muscle mass. In literature, limited data exist regarding body composition and chemosensitivity. Our results suggest a negative predictive role of visceral fat in tumor response to NC. In particular, the presence of visceral fat and internal fat tissue assessed from CT scan images is significantly associated with lower rate of pCR. In the subgroup of patients with pCR, 67% had normal visceral fat and 92% absence of fatty liver disease, respectively.

Table 2 Body Composition Parameters In Overall Population And According To Menopausal Status

Body Composition Parameters	All Patients		Premenopause		Postmenopause		P Value
Patients	137		66		71		
	N	%	n	%	n	%	
SFA (cm ²)							0.403
normal	8	6	5	8	3	4	
high	129	94	61	92	68	96	
VFA (cm ²)							<0.0001
normal	73	53	52	79	21	30	
high	64	47	14	21	50	70	
LMCA (cm ² /m ²)							0.828
sarcopenia	48	36	25	45	23	43	
normal	62	46	31	55	31	57	
unknown LMCA	27	18	10		17		0.017
liver/spleen ratio					Not		
fatty liver disease	24	18	6	9	18	25	
normal	113	82	60	91	53	75	
Obesity disease (BMI ≥ 25 & VFA ≥ 100)							<0.0001
no	90	66	55	83	35	49	
yes	47	34	11	17	36	51	

Note: Significant *P*-values are shown in bold.

No association between subcutaneous fat and tumor response was found confirming that visceral fat tissue plays a more central role in chemo-resistance than other type of body fat. These evidences justify the absence of correlation between

Table 3 Results Of The Correlation Analyses For Body Composition Parameters And pCR Rate

Body Composition Parameters	Non-pCR Patients		pCR Patients		p Value
Patients (n)	98		39		
	n	%	n	%	
SFA (cm²) normal high	6 92	6 94	2 37	5 95	0.823
VFA (cm²) normal high	47 51	48 52	26 13	67 33	0.048
LMCA(cm²/cm³) sarcopenia normal unknown LMCA	34 47 27	42 58	14 15	48 52	0.557
Liver/Spleen ratio fatty liver disease normal	21 77	21 79	3 36	8 92	0.056
Obesity disease (BMI ≥25 and VFA ≥100) yes no	62 36	63 37	28 11	72 28	0.341

Note: Significant *P*-values are shown in bold.

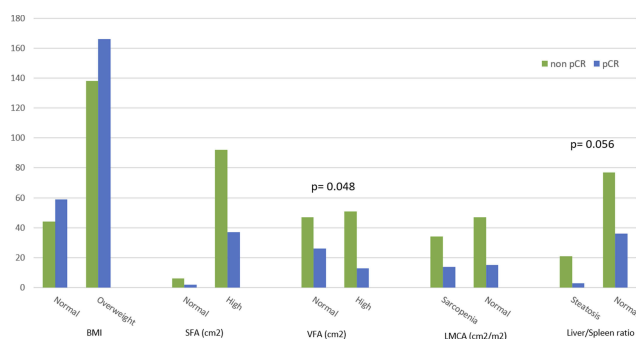


Figure 2 pCR rate according to body distribution parameters and BMI.

BMI measure and pCR rate found in our study, too. In fact, BMI value does not account for differences in body composition. It is known how patients with high BMI can be sarcopenic and how patients with normal BMI can have visceral and intra-visceral fat deposits. In literature, data on the predictive role of BMI are extremely controversy. In a large study conducted by MD Anderson Cancer Center, the pCR rate was significantly lower in overweight patients compared to normal/underweight ones.¹⁵ Although, a metaanalysis based on eight major trials found no association between BMI measure and tumor sensitivity.¹⁶

Postmenopausal status is a known cause of changes in body fat distribution, mainly increasing visceral fat tissue.^{17,18} In our study population, postmenopausal status was significantly associated with overweight, high VFA and fatty liver compared to premenopausal women. Fat tissue is rich in aromatases, enzyme able to convert androgens to estrogens. It is well demonstrated that overweight women have a higher level of estrogens compared to normal weight patients.¹⁸ These clinical data can explain the increased number of HR+ BC in overweight women compared to normal weight ones founded in our analysis.

Regarding sarcopenia and pCR rate, no relationship was found in our study. That result must be interpreted with caution considering the small number of patients found to be sarcopenic in our study population. Data from a retrospective study suggested a positive predictive and prognostic value of sarcopenia in the subgroup of normal weight women.⁷ The reason for this benefit was explained by the relatively higher chemotherapy dose used in that subgroup of patients. On the contrary, evidence on sarcopenia and tumor other than BC identified a strong association between sarcopenia, cachexia syndrome and worse survival outcomes.¹⁹

This analysis has some limitations particularly because it is a retrospective cohort study. Other limitation was that patients

staging with CT scan included a subgroup of women with more aggressive tumor with a higher risk of metastatic spread compared to women staged with liver-ultrasound and chest x-ray. This selection could justify the absence of association between BCPs and survival outcomes. Finally, 7% of overweight patients received a chemotherapy dose reduction due to their high body surface area that could be a bias in the evaluation of tumor response to chemotherapy.

Conclusion

Fat tissue is strongly involved in BC tumorigenesis inducing insulin resistance, chronic inflammation and hormonal changes.⁵ In particular, visceral adipose tissue seems to have more pro-cancer activity than other adipose tissue.¹⁴ The evaluation of BCPs is the best way to assess the real body composition. BMI alone cannot account for neither differences in fat distribution nor type of body fat. Our finding confirms the evidence that visceral fat is more involved in cancer cells homeostasis than other adipose tissue. High levels of visceral and intra-visceral fat significantly influence chemosensitivity. The rate of pCR is significantly lower in patients with visceral adiposity and steatosis. To improve efficacy of treatment is essential to clarify the relationship among adiposity, treatment sensitivity and survival outcomes.

Ethics Approval And Informed Consent

The institutional review board of AOU Policlinico of Modena approved this retrospective study and waived the need to obtain informed consent from the patients.

Disclosure

The authors report no conflicts of interest in this work.

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